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Phosphoric and Phosphinic Sulfonic Anhydrides – Reinvestigation and Corrections. Novel Methods of Synthesis

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Earlier works from this and other laboratories on phosphoric and phosphinic sulfonic anhydrides have been reinvestigated. It was found that no single reaction described in the past provides a general method for the production of mixed anhydrides $RR'P(O)SO_2R''$ (**3**) in high yields of isolated products. The following three efficient synthetic procedures leading to pure anhydrides **3** are described: a) Trifluoromethanesulfonic acid promoted reaction of phosphinic acid **9** with sulfonic triazolides **10**. b) Reaction of phosphinic and phosphoric imidazolides **13** with sulfonic acid **6**. c) Reaction of **13** with sulfonic anhydride **15**. All methods result in high yields. Some chemical properties of the anhydrides **3** are described.

Phosphorsäure- und Phosphinsäure-sulfonsäure-anhydride – Neuuntersuchung und Korrekturen. Neue Synthese-Methoden

Frühere Ergebnisse aus unseren und anderen Laboratorien an Phosphorsäure- und Phosphinsäure-sulfonsäure-anhydriden wurden überprüft. Es wurde jetzt gefunden, daß sich keine einzige früher beschriebene Reaktion als allgemeine Methode zur Darstellung gemischter Anhydride $RR'P(O)SO_2R''$ mit hohen Ausbeuten an isolierten Produkten eignet. Die folgenden drei Verfahren zur Synthese von reinen Anhydriden **3** werden beschrieben: a) Die Trifluormethansulfonsäure-katalysierte Reaktion von Phosphinsäure **9** mit Sulfonsäure-triazoliden **10**. b) Reaktion von Phosphinsäure- und Phosphorsäure-imidazoliden **13** mit der Sulfonsäure **6**. c) Umsetzung von **13** mit Sulfonsäureanhydrid **15**. Alle Methoden ergeben hohe Ausbeuten. Einige chemische Eigenschaften der Anhydride **3** werden beschrieben.

There is a continuing and considerable interest in the chemistry and biochemistry of phosphorus mixed anhydrides. Mixed anhydrides of phosphoric-sulfur acids are of fundamental interest in the transfer of sulfate. for example 3'-phosphoadenine-5'-phosphosulfate (PAPS) serves as the active sulfuryl donor in the formation of sulfate esters[1]. In synthetic oligonucleotide chemistry, phosphoric sulfonic anhydrides are postulated as reactive intermediates[2]. Such anhydrides were recently suggested as intermediates in biooxydation of thiolophosphates[3]. Also chiral thio-phosphonic and -phosphinic sulfonic anhydrides are of great interest as models for studying mechanisms and stereochemistry of displacement at tetracoordinated phosphorus center[4].

Satisfactory syntheses of full esters of phosphoric sulfonic anhydrides $RR'(P)OSO_2R''$ have not been available until now most likely due to their high reactivity towards nucleophiles. This reactivity explains the failure of early attempts by *Corby* and *Kenner* to obtain mixed anhydrides

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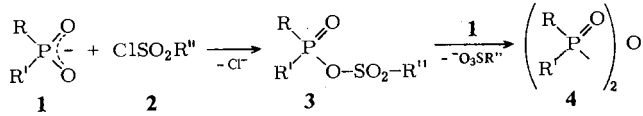
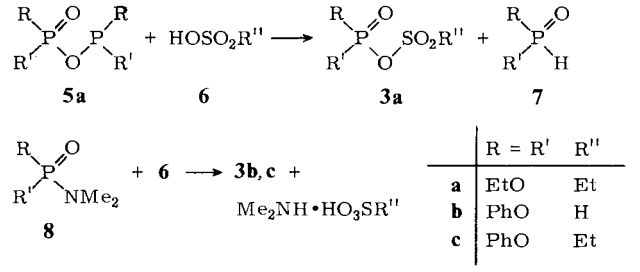
3 by a condensation reaction starting from organic sulfonyl chlorides and phosphate anion as shown in Scheme 1 [5].

Scheme 1



1 **2** **3** **4**

The above mentioned work led to the isolation of the pyrophosphate **4** as the only phosphorus containing product. Attempts to synthesize similar mixed anhydrides by condensation reactions based on Scheme 1 were undertaken in this laboratory. The results obtained were the same as those observed by earlier workers. Even the use of bulky substituents attached to the phosphorus atom (R = tBu) did not yield the desired mixed anhydride **3** and led to the pyrophosphate **4**. In spite of steric hindrance the rate of the nucleophilic displacement reaction at the phosphorus center in **3** (R = tBu) by the anion **1** leading to **4**, seems to be considerably higher than that of the condensation reaction leading to **3** [6]. The early work from this laboratory [7] relating to the synthesis of **3a** based on the reaction of phosphoric phosphorous anhydride **5a** with sulfonic acid **6** was reinvestigated.



	R = R'	R''
a	EtO	Et
b	PhO	H
c	PhO	Et

We demonstrated by ^{31}P NMR spectroscopy that these results were not completely correct. However, we were able to confirm the formation of the phosphoric sulfonic anhydride **3a** in this reaction, but in lower concentrations compared to other products present in the reaction mixture, such as pyrophosphate. It was not possible to isolate the mixed anhydride **3a** as previously claimed [7]. In the work reported by *Skrowaczewska* and co-workers in which the reaction between phosphoramidates **8** and sulfonic acids was described [8], the purity of the phosphoric sulfonic anhydrides **3b, c** was not indicated. This method has been also reinvestigated in the frame of the present work and the purity of anhydrides **3** based on ^{31}P NMR spectroscopy never exceeded 60%.

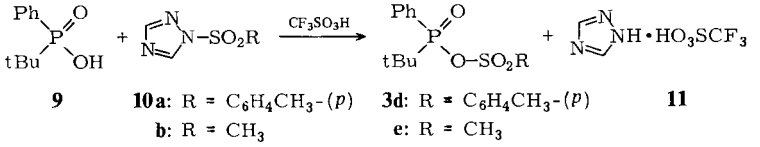
The work to be presented below concerns novel methods for the synthesis of phosphoric and phosphinic sulfonic anhydrides which lead to isolable products of high purity.

Synthesis of Anhydrides 3 via Triazolides of Sulfonic Acids

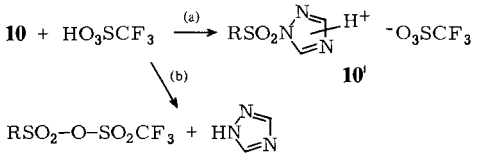
Sulfonic triazolides, equally imidazolides and tetrazolides, are used in oligonucleotide synthesis as "activating agents" [9]. In the method described here the mixed anhydrides **3d, e** are obtained by the reaction of phosphinic acid **9** with sulfonic triazolides **10** in the presence of equimolar amounts of trifluoromethanesulfonic acid.

Trifluoromethanesulfonic acid in this proportion is necessary for the reaction to proceed to completion. In the absence of strong acid no reaction was observed even after an extended reaction time. There are two possible explanations which could account for the role of CF_3SO_3H in the reaction.

Trifluoromethanesulfonic acid can be considered as an activating agent which could lead to the formation of protonated sulfonic triazolide **10'** (reaction a) or to the mixed sulfonic anhydride **12** (reaction b). The formation of **12** seems to be highly unfavourable because of the low nucleophilicity of the $CF_3SO_3^-$ anion.



9 **10a**: R = $C_6H_4CH_3$-(*p*) **3d**: R = $C_6H_4CH_3$-(*p*) **11**
b: R = CH_3 **e**: R = CH_3



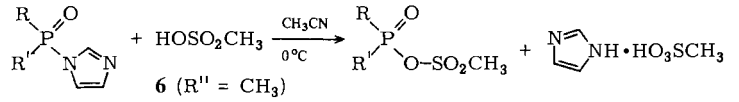
10'

12

This conclusion was supported by the results of conductometric studies. Measurements of the conductivity of a solution of methanesulfonic triazolide **10b** titrated with a solution of trifluoromethanesulfonic acid showed an inflection point at the reagents molar ratio 1:1. This result suggests the formation of protonated sulfonic triazolide **10'**. The formation of the mixed anhydride **12** would give the inflection point at the reagents molar ratio 2:1. The role of trifluoromethanesulfonic acid then must be to protonate the triazolide ring system in triazolides **10** which creates an excellent leaving group. The presence of CF_3SO_3H also retards ionization of the phosphinic acid **9** causing it to remain in its protonated form. The phosphorus hydroxyl group is sufficiently nucleophilic for an S_N2 reaction at the sulfur atom of the protonated triazolide **10'** forming the phosphinic sulfonic anhydrides **3d,e** and most likely is too weak a nucleophile to attack efficiently the anhydrides **3** which would result in a pyrophosphate end product. In fact the pyrophosphate product is observed in the reaction mixture, but as the minor component. Triazolium trifluoromethanesulfonate (**11**) precipitates from the reaction medium. The method described above is well suited for the preparation of anhydrides **3** with steric hindrance at the phosphorus center.

Synthesis of Anhydrides 3 via Imidazolides of Phosphorus Acids

The use of phosphinic and phosphoric imidazolides **13** in the syntheses of the mixed anhydrides **3e–g** can be considered as an extention of the method proposed by *Skrowaczewska* et al.[8], which takes advantage of the lability of the P – N bond in acid medium.

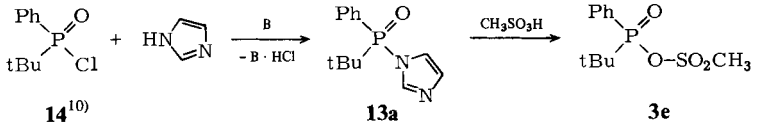


6 ($R'' = CH_3$)

	R	R'
13a	Ph	tBu
b	iPrO	iPrO
c	EtO	EtO

	R	R'
3e	Ph	tBu
f	iPrO	iPrO
g	EtO	EtO

The active intermediate is likely to be a protonated form of the imidazole **13**. The imidazolium salt of sulfonic acid precipitates from the reaction mixture. The high reactivity of imidazolides **13** and the ease of product isolation make this procedure a method of choice in many cases. This reaction enables the synthesis of optically active phosphinic sulfonic anhydrides (e.g. **3e**) via optically active imidazolides of phosphorus acids. The optically active imidazolide **13a** was synthesized starting from optically active phosphinyl chloride **14**[10].

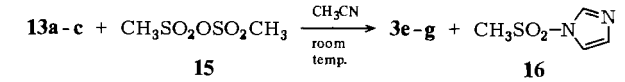


14[10] $[\alpha]_D^{20} = +27.4°$ (benzene)

13a $[\alpha]_D^{20} = -1.5°$ (benzene)

3e $[\alpha]_D^{20} = +6.2°$ ($CHCl_3$)

Some problems arise in the method described above that are related to the preparation and use of anhydrous sulfonic acids. These difficulties can be avoided if instead of free sulfonic acids **6** the anhydride of the appropriate acid **15** is employed.



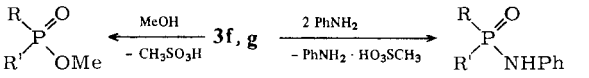
15 **16**

The sulfonic imidazolide **16** which formed during the reaction is removed by precipitation upon concentration of the reaction mixture. The residue consists of pure mixed anhydrides **3e–g**. This method can be recommended in the synthesis of mixed anhydrides which are liquids.

Final Remarks

In all cases the purity of **3** was determined by ^{31}P NMR, ^{1}H NMR and IR spectroscopy. The ^{31}P chemical shifts of phosphoric and phosphinic sulfonic anhydrides are very close to those of the corresponding pyrophosphate systems. This facts must be taken into account in studies of systems in which both structures may be formed or interconverted. All reactions described above leading to mixed anhydrides **3** proceed in high yields. To leave no doubt about the chemical identity of the anhydrides **3** they were

allowed to react with methanol and aniline. The reaction products, methyl esters **17**, anilides **18**, and the corresponding sulfonium salts formed in almost quantitative yields were identical with authentic samples.



17a, b **a**: R = R' = iPrO **18a, b**
b: R = R' = EtO

At this point it is necessary to emphasize the high reactivity of the mixed anhydrides **3**, especially of those without a sterically hindered phosphorus atom.

Experimental Part

All m.p. are uncorrected. All solvents and commercial reagents were dried or purified by conventional methods just before use. – NMR spectra: Perkin Elmer R-12B and Jeol FX60 Spectrometer, TMS or H_3PO_4 (96%) as standards. – Microanalyses: Microanalysis Laboratory of Centre of Molecular and Macromolecular Studies, Łodz, Boczna 5.

Materials: Starting materials and authentic samples such as *tert*-butylphenylphosphinic acid (**9**), diisopropyl phosphate, diethyl phosphate, *tert*-butylphenylphosphinyl chloride (**14**), diisopropyl phosphorochloridate, diethyl phosphorochloridate, diisopropyl and diethyl *N*-phenylphosphoramidate (**18a, b**), diethyl methyl phosphate (**17b**), diisopropyl methyl phosphate (**17a**), methanesulfonic anhydride (**15**), and 1-(4-methylphenylsulfonyl)-1*H*-1,2,4-triazole (**10a**) were synthesized according to the methods given in the literature[11]. the purity was confirmed by ^1H and ^{31}P NMR spectroscopy.

Preparation of the imidazolides **13**: A mixture of triethylamine[12] (5.0 mmol) and imidazole (5.0 mmol) dissolved in anhydrous THF (100 ml) was added dropwise at 0°C to the solution of chloride **14** (5.0 mmol) in anhydrous THF (50 ml). After 2 h of stirring at room temp. the precipitate was removed by filtration and the filtrate was concentrated. The product was purified by crystallization or by high-vacuum distillation.

1-(tert-Butylphenylphosphinyl)imidazole (**13a**): Yield 86%, m.p. 134–136°C (benzene/hexane). – ^1H NMR ($CDCl_3$): δ = 1.7 (d, 9H, tBu, J_{PHCH} = 18 Hz), 7.4–8.6 (m, 8H, aromatic). – ^{31}P NMR ($CDCl_3$): δ = +42.8.

$C_{13}H_{17}N_2OP$ (264.2) Calcd. C 62.9 H 6.9 N 11.2 P 12.4
Found C 63.2 H 7.2 N 11.2 P 12.2

1-(Diisopropoxyphosphinyl)imidazole (**13b**): Yield 79%, b.p. 75°C/0.15 Torr. – ^1H NMR ($CDCl_3$): δ = 1.5 (d, 12H, $CH(CH_3)_2$, J_{HH} = 6 Hz), 4.5–5.2 (m, 2H, $CHMe_2$); imidazole ring 7.3 (s, 1H), 7.6 (s, 1H), 8.2 (s, 1H). – ^{31}P-NMR ($CDCl_3$): δ = –8.3.

$C_9H_{17}N_2O_3P$ (232.2) Calcd. C 46.6 H 7.3 N 12.1 P 13.4
Found C 47.0 H 7.0 N 12.0 P 13.2

1-(Diethoxyphosphinyl)imidazole (**13c**): In this case triethylamine was replaced by triisopropylamine. Yield 98% (by ^1H and ^{31}P NMR spectroscopy). – ^1H NMR ($CDCl_3$): δ = 1.3–1.9 (t, 6H, CH_3), 4.2–4.9 (m, 4H, OCH_2), imidazole ring 7.3 (s, 1H), 7.6 (s, 1H), 8.2 (s, 1H). – ^{31}P NMR ($CDCl_3$): δ = –6.4.

Reaction of phosphinic acid **9** *with sulfonic triazolides* **10** *in the presence of trifluoromethanesulfonic acid:* To the solution of **10a** or **b** (6.0 mmol) in dry acetonitrile (20 ml), maintained at 0°C, a solution of trifluoromethanesulfonic acid (6.0 mmol) in dry acetonitrile (20 ml) was added. Then *tert*-butylphenylphosphinic acid (**9**) (6.0 mmol) in dry acetonitrile (20 ml) was added at room temperature. After 3 h of stirring at room temperature the resulting precipitate was filtered off and the filtrate was concentrated. All solid products were purified by crystallization.

tert-Butylphenylphosphinic 4-methylbenzenesulfonic anhydride (**3d**): Yield 68%, m.p. 126–128°C (benzene/hexane). – ^{1}H NMR ($CDCl_3$): δ = 1.6 (d, 9H, tBu, J_{PCCH} = 18 Hz), 2.8 (s, 3H, CH_3), 7.6–8.7 (m, 9H aromatic). – ^{31}P NMR ($CDCl_3$): δ = +55.4.

$C_{17}H_{21}O_4PS$ (352.2) Calcd. C 57.9 H 6.0 P 8.8 Found C 57.5 H 6.2 P 8.6

tert-Butylphenylphosphinic methanesulfonic anhydride (**3e**): Yield 58%, m.p. 102–104°C (benzene/hexane). – ^{1}H NMR ($CDCl_3$): δ = 1.7 (d, 9H, tBu, J_{PCCH} = 17 Hz), 3.7 (s, 3H, CH_3), 7.7–8.8 (m, 5H aromatic). – ^{31}P NMR ($CDCl_3$): δ = +53.7.

$C_{11}H_{17}O_4PS$ (276.1) Calcd. C 47.8 H 6.2 P 11.2 S 11.6
Found C 47.7 H 6.2 P 11.5 S 11.5

Reaction of imidazolides **13** *with methanesulfonic acid* (**6**, R'' = CH_3): To the solution of **13a, b, c** (5.0 mmol) in dry acetonitrile (20 ml) a solution of methanesulfonic acid (10 mmol) in dry acetonitrile (20 ml) was added at 0°C. The reaction mixture was stirred 2 h at room temperature. Then the precipitate was filtered off. The resulting filtrate was worked up as described above:

3e: Yield 92%, m.p. 98–99°C (benzene/hexane), identical with the product obtained above according to spectral data.

Imidazole salt of methanesulfonic acid: m.p. 195–198°C.

$C_4H_8N_2O_3S$ (164.1) Calcd. C 29.3 H 4.9 N 17.1 S 19.5
Found C 29.0 H 4.7 N 17.3 S 19.0

Methanesulfonic phosphoric anhydride, diisopropyl ester (**3f**): Yield 100% (by ^{1}H and ^{31}P NMR spectroscopy). – ^{1}H NMR (neat): δ = 1.7 (d, 12H, $CH(CH_3)_2$, J_{HH} = 6 Hz), 3.8 (s, 3H, CH_3), 4.9–5.5 (m, 2H, $CHMe_2$). – ^{31}P NMR (neat): δ = −15.6.

Imidazole salt of methanesulfonic acid: m.p. 198–200°C.

Methanesulfonic phosphoric anhydride, diethyl ester (**3g**): Yield 100% (by ^{1}H and ^{31}P NMR spectroscopy). – ^{1}H NMR (neat): δ = 1.5–2.0 (t, 6H, CH_3), 3.8 (s, 3H, SO_2CH_3), 4.4–5.1 (m, 4H, OCH_2). – ^{31}P NMR (neat): δ = −13.6.

Imidazole salt of methanesulfonic acid: m.p. 196–198°C.

Reaction of imidazoles **13** *with methanesulfonic anhydride* (**15**): A solution of **15** (5.0 mmol) in dry acetonitrile (10 ml) was added dropwise at room temperature to the solution of **13a–c** (5.0 mmol) in anhydrous acetonitrile (10 ml). Afterwards the mixture was stirred at room temperature for 1 h more, filtrated, and worked up in the usual manner. The reaction products were separated by column chromatography (Mercka Silica gel Art No 7754) using chloroform/acetone (2:1) as eluent.

3e: Yield 60%, m.p. 98–100°C, spectral data as above.

1-(Methylsulfonyl)imidazole (**16**): Yield 42%, m.p. 92–94°C. – ^{1}H NMR (CD_3COCD_3): δ = 3.4 (s, 3H, CH_3), 7.0 (s, 1H), 7.4 (s, 1H), 7.9 (s, 1H).

$C_4H_6N_2O_2S$ (146.1) Calcd. C 32.9 H 4.1 N 19.2 S 21.9
Found C 32.8 H 4.5 N 18.9 S 21.5

3f: Yield 100% (by ^1H and ^{31}P NMR spectroscopy).
3g: Yield 100% (by ^1H and ^{31}P NMR spectroscopy).

Reaction of mixed anhydrides **3f,g** *with methanol:* Into an excess of anhydrous methanol, maintained at room temp., **3f** or **g** was added. After 1 h methanol was removed under reduced pressure. The reaction product was purified by distillation.

Diisopropyl methyl phosphate (**17a**): Yield 98%, b.p. 30–32°C/0.05 Torr. – ^1H NMR (neat): δ = 1.6 (d, 12H, $CH(CH_3)_2$, J_{HH} = 6 Hz), 4.0 (d, 3H, OCH_3, J_{POCH} = 9 Hz), 4.6–5.3 (m, 2H, $CHMe_2$). – ^{31}P NMR (neat): δ = +1.7.

$C_7H_{17}O_4P$ (196.2) Calcd. C 42.8 H 8.8 P 15.8 Found C 42.8 H 8.9 P 15.8

Methanesulfonic acid: Yield 100%, b.p. 60–62°C/0.05 Torr. – ^1H-NMR (neat): δ = 3.4 (s, 3H, CH_3).

$C_1H_4O_3S$ (96.1) Calcd. C 12.5 H 4.2 S 33.4 Found C 12.5 H 4.0 S 33.2

Diethyl methyl phosphate (**17b**): Yield 99%, b.p. 25°C/0.05 Torr. – ^1H NMR (neat): δ = 1.5–1.9 (t, 6H, CH_2CH_3), 4.1 (d, 3H, CH_3, J_{POCH_3} = 9 Hz), 4.3–4.8 (m, 4H, CH_2). – ^{31}P NMR (neat): δ = –0.8.

$C_5H_{13}O_4P$ (168.1) Calcd. C 35.7 H 7.8 P 18.4 Found C 35.6 H 7.5 P 18.2

Methanesulfonic acid: Yield 91%, b.p. 60°C/0.05 Torr.

Reaction of **3f,g** *with aniline:* A solution of **3f,g** (10 mmol) in anhydrous benzene (10 ml) was added at +15°C to anhydrous aniline (10 mmol) in anhydrous benzene (10 ml). The reaction mixture was kept 1 h at room temp., then the precipitate was filtered off and washed with chloroform (2 × 10 ml). Joined organic solutions were concentrated under reduced pressure. The reaction products were isolated and purified by crystallization from pentane.

Diisopropyl N-phenylphosphoramidate (**18a**): Yield 97%, m.p. 122.5–124°C. – ^1H NMR ($CDCl_3$): δ = 1.8 (d, 12H, $CH(CH_3)_2$, J_{HH} = 7 Hz), 4.7–5.5 (m, 2H, $CHMe_2$), 7.8–8.0 (m, 5H aromatic and NH). – ^{31}P NMR ($CDCl_3$): δ = +0.9.

$C_{12}H_{20}NO_3P$ (257.1) Calcd. C 56.0 H 7.9 P 12.1 N 5.4
Found C 56.1 H 7.7 P 12.1 N 5.3

Aniline salt of methanesulfonic acid: Yield 91%, m.p. 210–212°C.

$C_7H_{11}NO_3S$ (189.2) Calcd. C 44.4 H 5.9 N 7.4 S 16.9
Found C 44.4 H 6.2 N 7.1 S 16.7

Diethyl N-phenylphosphoramidate (**18b**): Yield 98%, m.p. 94–96°C (*n*-pentane). – ^1H NMR ($CDCl_3$): δ = 1.6–2.2 (q, 6H, CH_3), 4.3–5.1 (m, 4H, CH_2), 7.3–8.1 (m, 5H aromatic and NH). – ^{31}P NMR ($CDCl_3$): δ = +2.0.

$C_{10}H_{16}NO_3P$ (229.2) Calcd. C 52.4 H 7.0 N 6.1 P 13.5
Found C 52.4 H 7.1 N 6.2 P 13.3

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[12] 1-(Diethoxyphosphinyl)imidazole (**13c**) was prepared according to the method as described. In this case triethylamine was replaced by triisopropylamine.

[298/81]